A NOVEL FUZZY NEURAL NETWORK ESTIMATOR FOR PREDICTING HYPOGLYCAEMIA IN INSULIN-INDUCED SUBJECTS

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Abstract- **Predicting the onset of hypoglycaemia can avoid major health complications in Type 1 insulin-dependent-diabetes-mellitus (IDDM) patients. This paper describes the design of a novel fuzzy neural network estimator algorithm (FNNE) for predicting the glycaemia profile and onset of hypoglycaemia in insulin-induced subjects, by modelling the changes in heart rate and skin impedance parameters. Hypoglycaemia was induced briefly in 12 volunteers (group A: 6 non-diabetic subjects and group B: 6 Type 1 IDDM patients) using insulin infusion. Their skin impedances, heart rates and actual blood glucose levels (BGL) were monitored at regular intervals. The FNNE algorithm was trained using all subjects from group A and validated/tested on the remaining subjects from group B. The mean error of estimation of BGL profile for the training data set (group A) was 0.107 ($\rho <$ 0.05) and for the validation/test data set (group B) was 0.139 ($\rho <$ 0.05). Furthermore, the FNNE algorithm was able to predict the onset of hypoglycaemia episodes in group A and group B with a mean error of 0.071 ($\rho < 0.03$) and 0.176 ($\rho < 0.05$) respectively.**
Keywords - **Hypoglycaemia, heart rate, skin impedance**

I. INTRODUCTION

For patients with Type 1 insulin-dependent-diabetes-mellitus (IDDM), hypoglycaemia is a frequent and severe complication [1]. Introduction of intensive therapy with continuous subcutaneous insulin infusion pumps and frequent daily injections has led to an increase in hypoglycaemia episodes [2]. Past studies have shown that intensive therapy can lower the glucose threshold for neurogenic warning symptoms, which exposes IDDM patients to further risks associated with severe hypoglycaemia [3].

The glycaemic levels within the human body reflect onto the symptomatic changes of certain physiological parameters [4-5]. The most profound physiological disturbances are caused by the activation of the sympathetic nervous system, which reflect through to the parameters such as sweating and cardiovascular system response. Sweating is primarily due to cholinergic sympathetic activity [6] and cardiovascular system response is due to the increase in heart rate and stroke volume [7]. As a result certain experiments have been undertaken to analyse the correlation between the measured parameters and blood glucose levels (BGL) within the body [8-9]. However, no attempts have been made to estimate BGL profiles or the severity of hypoglycaemia based on the changes in the measured parameters.

This paper describes the design of a fuzzy neural network estimator (FNNE) algorithm which is used for predicting glycaemic profiles and hypoglycaemia episodes in insulin-induced subjects. This FNNE algorithm only uses heart rates and skin impedances as system inputs. It comprises of a parallel fuzzy inference engine and a multi-layered neural network system with trainable weight matrix for transforming these measured physiological parameters into estimated blood glucose levels.

II. METHODOLOGY

Twelve subjects, 6 non-diabetics (group A) and 6 Type 1 IDDM (group B) subjects aged 26 ± 3 years, volunteered for this study after giving informed consent. The sample population consisted of 6 males and 6 females. The study was approved by the local Ethics Committee. All subjects were non-obese as assessed by their height: 1.69 ± 0.08 m, weight: 68 ± 10 kg, and body surface area of 1.74 ± 0.23 m^2. The experiments were conducted in morning periods at the Diabetes Centre, Prince of Wales Hospital clinical research laboratory. All subjects were required to fast from midnight.

Two sets of skin surface electrodes, which interfaced directly to the measuring instrument, were attached to the subject to measure the physiological parameters, heart rate and skin impedance [10]. Intravenous Teflon cannulae were inserted into a vein in each forearm and kept patent using a saline drip. The cannula on the right forearm was used for intravenous infusion of insulin (Actrapid, Novo Nordisk) set at a rate of 40 mU/kg/hour.

Thirty minutes before commencing insulin infusion, baseline measurements of BGL were collected at 15-min. intervals. At the end of this 30-min. *baseline phase*, the insulin infusion commenced at a flow rate of 10 ml/hr, marking the beginning of the *data-logging phase* for a duration of 90 min. During this phase, BGL was collected at 5-min. intervals while the instrument logged at 1min intervals.

III. ALGORITHM DESIGN

A. Initial data processing

The measured physiological parameters (heart rate and skin impedance) were first normalised to enhance the cross-correlation of the algorithm and to counteract varying environmental conditions which could affect the measurement process. The processing unit then collated the measured heart rate and skin impedance parameters (measured at 1 sample per min.) with actual measured BGL data (measured at 1 sample per 5 min.), using a weighted average method.

As a result, a generalised data matrix set Y_s which consists of heart rates X_{hr_s} skin impedances X_{si_s} and measured BGLs $X_{BGL_s}^{act}$ was formed:

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Abstract

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$$Y_s = \begin{bmatrix} X_{hr\,s} & X_{si\,s} & X_{BGL\,s}^{act} \end{bmatrix} = \begin{bmatrix} \overline{x}_{11} & \overline{x}_{12} & x_{13} \\ \overline{x}_{21} & \overline{x}_{22} & x_{23} \\ \vdots & \vdots & \vdots \\ \overline{x}_{j1} & \overline{x}_{j2} & x_{j3} \\ \vdots & \vdots & \vdots \\ \overline{x}_{n1} & \overline{x}_{n2} & x_{n3} \end{bmatrix}_{(nx3)} \quad (1)$$

where n corresponds to the population size i.e. 20 for the sth subject ($s = 1,2…12$).

B. Fuzzy neural network estimator (FNNE)

The FNNE algorithm is based on a parallel combination of fuzzy inference mechanism (FIM) and a multi-layered neural network (NN) architecture with trainable weight matrix to transform the measured physiological parameters, $X_{hr\,s}$ and $X_{si\,s}$ into an estimated BGL profile, $X_{BGL\,s}^{est}$ for each subject ($s = 1,2…12$). This FNNE algorithm benefits from the linguistic rule modelling behaviour of the FIM and the trainable characteristics of the multi-layered NN algorithm. Its architecture is shown in Figure 1.

The core principle of the FNNE algorithm is based on the first-order Sugeno fuzzy model [11-12] where the FIM is compiled on a set of N fuzzy *if-then* rules. These rules are mainly derived using a deterministic approach with medical advice by experts in the field of diabetes study. The kth rule has the following format:

Rule k: if $\overline{x}_{j1}$ is VH and $\overline{x}_{j2}$ is BN then $x_{j3}^{est} = f_k(\overline{x}_{j1}, \overline{x}_{j2})$ (2)

where VH (Very High) and BN (Below Normal) are the linguistic variables associated with the fuzzy subsets of $\overline{x}_{j1}$, $\overline{x}_{j2}$, and $f_k(\overline{x}_{j1}, \overline{x}_{j2}) = \beta_{k0} + \beta_{k1}\overline{x}_{j1} + \beta_{k2}\overline{x}_{j2}$ is the resulting first-order consequent polynomial function for calculating the jth estimated BGL value, x_{j3}^{est} (from $X_{BGL\,s}^{est}$ data set).

The resulting FNNE algorithm produces (through the training process of the first and second phase) a solution for all N polynomial function coefficients ($\beta_{k0}, \beta_{k1}, \beta_{k2}$, for $k = 1,..,N$), collated into a coefficient matrix B, represented as:

$$\text{B}_{coeff} = \begin{bmatrix} \beta_{10} & \beta_{11} & \beta_{12} \\ \beta_{20} & \beta_{21} & \beta_{22} \\ \vdots & \vdots & \vdots \\ \beta_{k0} & \beta_{k1} & \beta_{k2} \\ \vdots & \vdots & \vdots \\ \beta_{N0} & \beta_{N1} & \beta_{N2} \end{bmatrix}_{(N\times3)} \quad (3)$$

where the kth row $\beta_k = \begin{bmatrix} \beta_{k0} & \beta_{k1} & \beta_{k2} \end{bmatrix}$ is the coefficient data set for the kth polynomial function $f_k(\overline{x}_{j1}, \overline{x}_{j2})$.

Layer 1 consists of the fuzzification layer which maps the jth ($j= 1,2…n$) normalised measured heart rate value $\overline{x}_{j1}$, and

skin impedance value $\overline{x}_{j2}$ within $X_{hr\,s}$, $X_{si\,s}$ ($s = 1,2,…12$) into corresponding new fuzzy sets [13].
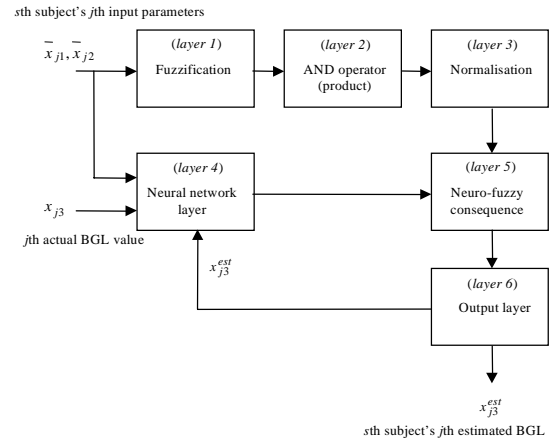

Fig. 1: FNNE block diagram

Layer 2 performs the *AND* operation on all corresponding linguistic variables (derived by fuzzification) associated with each *if-then* rule. *Layer 3* normalises each firing strength node from layer 2, based on the sum of all rules (N rules).

The neural network layer (*layer 4*) performs the feed-forward network process of the jth values $\overline{x}_{j1}$ and $\overline{x}_{j2}$, together with the actual jth BGL value x_{j3} as feedback error. Using this neural network structure, *layer 4* uses all N estimated polynomial function coefficients ($\beta_{k0}, \beta_{k1}, \beta_{k2}$, for $k = 1,..,N$) to produce N output neurons which will be processed by the neuro-fuzzy consequence layer (*layer 5*). *Layer 5* is the central layer within the FNNE architecture. This layer performs the neuro-fuzzy consequence operation where each output is the product of the normalised firing strength (output from *layer 3*) by the corresponding output neuron from the neural network layer (*layer 4*). Finally, the output layer (*layer 6*) provides the jth estimated BGL output, x_{j3}^{est}, by summing the all neuro-fuzzy consequence output nodes generated by *layer 5*.

Using the general delta-learning rule [14], during each qth iteration, the coefficients within B_{coeff} are updated in such a manner to minimise the overall jth error $E_j = 1/2(x_{j3} - x_{j3}^{est})^2$. Using the steepest descent technique, these coefficients are updated according to:

$$\beta_k^{q+1} = \beta_k^q - \eta\nabla E_j(\beta_k)x_j \quad (4)$$

where η is a positive learning constant, $\nabla E_j(\beta_k)$ is the jth error gradient vector and $x_j = \begin{bmatrix} \overline{x}_{j1} & \overline{x}_{j2} & 1 \end{bmatrix}$ is the jth observation within Y_s ($s = 1,2,…6$) (training using group A only). At the end of each qth iteration, the validation data sets $X_{hr\,s}$, $X_{si\,s}$ and $X_{BGL\,s}^{act}$ ($s = 7, 8$) in group B are used to determine the cycle error (estimated BGL x_{j3}^{est}, with respect to

the measured BGL x_{j3}) and its rate of convergence. The trained and optimised FNNE algorithm is applied to the remaining subjects within group B (s = 9,10…12) with no further training to provide formal testing.

IV. RESULTS

A. Physiological parameter responses

The BGL profiles of both groups A and B are shown in Figure 2. In the baseline phase (-30 to 0 min interval), the means BGLs and ± standard deviation (SD) for groups A and B were 4.3 ± 0.4 mmol/l and 10.8 ± 1.4 mmol/l respectively. The minimum BGL value reached by group A was 1.93 ± 0.4 mmol/l, while the minimum value reached by group B was 1.5 ± 0.5 mmol/l within the time span of 60 minutes.
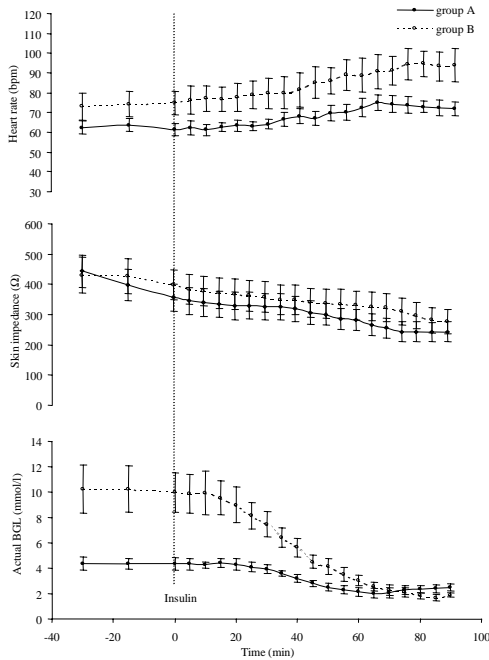

Fig. 2: Measured physiological parameter profiles

The resting heart rates at baseline phase for group A and group B had a mean of 62 ± 1 bpm (range 51 – 70 bpm) and 74 ± 2 bpm (range 63 – 94 bpm) respectively. During the severe hypoglycaemia phase, the heart rate for group A increased to a mean of 73 ± 7 bpm (range 63 – 80 bpm, mean increase of 11 bpm). Similarly, the heart rate for group B increased to mean of 95 ± 15 bpm (range 76 – 113 bpm, mean increase of 21 bpm).

The skin impedances at baseline phase for group A and group B had a mean of 400 ± 96 ohms (range 673 –172 ohms) and 417 ± 22 ohms (range 185 – 695 ohms) respectively. During severe hypoglycaemia episodes, the skin impedance for group A decreased to a mean of 276 ± 135 ohms (range 102 – 449 ohms). Similarly, the skin impedance for group B decreased to a mean of 306 ± 176 ohms (range 75 – 459 ohms).

B. FNNE algorithm response

The FNNE algorithm was trained using the data set of all subjects from group A (s = 1,2…6). The validation procedure was determined using the data obtained in the first two group B subjects (s = 7,8) and testing was conducted on the remaining four group B subjects (s = 9,10…12).

Figure 3 represents the combined correlated BGL data sets of all subjects in groups A and B (sample size n of 240). The solid linear line represents the correlation of estimated versus actual BGL data sets, and the two dashed lines represents the ± 5% deviation from this correlation. The BGL correlation of group A and group B produced an overall R^2 of 0.983.
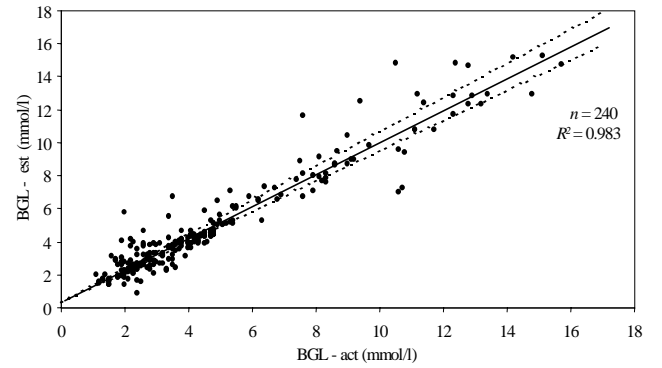

Figure 3: Combined correlated BGL plots

All subjects from group A demonstrated high correlation of estimated BGL (the mean multiple correlation coefficient, $\overline{R^2}$ = 0.986) with respect to actual BGL profile, $\rho < 0.05$ (mean likelihood probability). The overall mean error of estimation $\overline{\varepsilon}$ and a mean error of estimation for hypoglycaemia (BGL < 2.5 mmol/l) $\overline{\varepsilon}_{hypo}$ for group A were 0.107 ($\rho < 0.05$) and 0.071 ($\rho < 0.03$) respectively. The BGL estimation profiles of all subjects from group B correlated within the statistical confidence interval $\overline{R^2}$ = 0.979 ($\rho < 0.05$). The overall $\overline{\varepsilon}$ and $\overline{\varepsilon}_{hypo}$ for group B were 0.139 ($\rho < 0.05$) and 0.176 ($\rho < 0.05$).

Table 1 summarises the overall performance of the FNNE algorithm for both, group A and group B, including the multiple correlation coefficient, the estimated BGL value at hypoglycaemia and its time lead/ lag.

IV. DISCUSSION

This paper has introduced a novel fuzzy neural network estimator (FNNE) algorithm for modelling the non-linear correlation between measured physiological parameters and the actual BGL profile. This algorithm is based on a set of first-order estimation functions for estimating the BGL profiles and consequently, detecting the onset of hypoglycaemia episodes. These estimation functions were trained using controlled data sets of non-diabetic subjects (group A), and validated/tested using data sets obtained from Type 1 IDDM subjects (group B).

TABLE I
FNNE ALGORITHM PERFORMANCE SUMMARY

	Subject	R^2	ε	BGL (hypo) mmol/l	ε_{hypo}	t_{hypo} (min)
Group A	1	0.980	0.128	2.73	0.092	+ 5
	2	0.989	0.096	2.31	0.076	- 3
	3	0.990	0.094	2.63	0.052	+ 1
	4	0.992	0.091	2.54	0.016	+ 1
	5	0.987	0.098	2.52	0.001	+ 1
	6	0.979	0.137	2.94	0.176	+ 4
Group B	7	0.983	0.127	2.89	0.156	- 10
	8	0.988	0.112	2.78	0.113	+ 12
	9	0.985	0.122	2.77	0.108	*N/A*
	10	0.974	0.159	3.14	0.256	- 12
	11	0.976	0.146	2.97	0.188	+ 13
	12	0.971	0.165	2.88	0.152	+ 6

Analysing the static behaviour of the measured physiological parameters of all twelve subjects, a significant correlation was observed with respect to the measured BGL profile, $\rho < 0.01$. From the transition of normal glycaemic level (BGL above 3.5 mmol/l) to hypoglycaemia phase (BGL below 2.5 mmol/l), the mean heart rate of group A and group B increased by 11 and 21 bpm respectively. Similarly, the mean skin impedance of group A and group B decreased by 124 and 111ohms respectively. However, the variance of the measured physiological parameters and BGL values for group B were significantly larger than group A. This effect is primarily due to the irregular glucose counterregulatory present in Type 1 IDDM subjects system [1].

The FNNE was trained within 300 iterations of the training data set based on the convergence rate of the validation data set (subjects 7 and 8). The overall mean error of estimation $\bar{\varepsilon}$ and mean error of estimation of hypoglycaemia $\bar{\varepsilon}_{hypo}$ for group A were 0.107 ($\rho < 0.05$) and 0.071 ($\rho < 0.03$) respectively. The trained first-order estimation functions obtained from group A was validated and tested using group B data set. All group B subjects demonstrated good correlation of BGL estimation ($\bar{R^2}$ = 0.979), particularly below the 50-min. interval, $\rho < 0.055$. The overall $\bar{\varepsilon}$ and $\bar{\varepsilon}_{hypo}$ for group B were 0.139 ($\rho < 0.05$) and 0.176 ($\rho < 0.05$) respectively. The prediction time of hypoglycaemia varied from subject to subject with a mean prediction period of 9.7 ± 6.1 minutes of actual onset.

V. CONCLUSION

In order to improve the accuracy of the algorithm for estimating the BGL profile, further experiments are recommended, especially in the hypoglycaemia stage. Changing the first-order estimation functions to higher order functions (e.g. quadratic) may improve BGL estimation and provide better fitting equations. The size of the coefficient matrix will need to increase to accommodate higher-order functions. Increasing the number of estimation functions can improve the oscillation effects observed within group B. Other methods for improving BGL estimation may include larger training and validating sampling data set, adaptive training of membership functions and use of Hopfield neural network architecture to compensate for large time delays due to autonomic system response.

By addressing these issues with on-going research, an improved estimation procedure can be accomplished and implemented for the non-invasive detection of severe hypoglycaemia for patients with Type 1 diabetes.

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